

Imaging investigations before referral to a sarcoma center delay the final diagnosis of musculoskeletal sarcoma

Heidi Buvarp DYROP^{1,3}, Peter VEDSTED², Mathias RÆDKJÆR^{1,3}, Akmal SAFWAT¹, and Johnny KELLER¹

¹ Sarcoma Center of Aarhus University Hospital; ² The Research Unit for General Practice, Research Center for Cancer Diagnosis, Aarhus University; ³ Department of Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark.

Correspondence: heidi.dyrop@gmail.com

Submitted 2016-07-13. Accepted 2016-10-29.

Background and purpose — The use of point-of-care or local investigations before referral to specialist sarcoma centers as part of a fast-track diagnostic pathway varies, and may affect the time to diagnosis. We wanted to investigate differences in time intervals and proportion of malignancy in patients who were referred after initial diagnostic investigations were performed locally and in patients who were referred without these investigations.

Patients and methods — We included 545 consecutive patients who were referred to Aarhus Sarcoma Center for suspected musculoskeletal sarcoma. Data on time intervals and investigations performed were collected from questionnaires and patient records. Patients who were referred from outside Aarhus uptake area after initial MRI/CT or histology performed locally were compared with patients who were referred from Aarhus uptake area without these investigations.

Results — The median total interval from first symptom to diagnosis was 166 days for outside patients referred with MRI/CT or histology, which was 91 (95% CI: 76–106) days longer than for local patients who were referred without MRI/CT or histology. Comparing the same groups, the median diagnostic interval was 41 (95% CI: 30–51) days longer for outside patients including both primary care and hospital intervals. Both the proportion of malignancies (38% vs. 14%) and the proportion of sarcomas (24% vs. 7%) were higher in the outside group referred with MRI/CT or histology than in the local group without MRI/CT or histology.

Interpretation — Pre-referral investigations at a local hospital increased the diagnostic interval by at least 1 month for 50% of the patients, and the proportion of malignancy was more than doubled—to almost 40%. If investigations are to be performed before referral to a sarcoma center, they should be part of the fast-track pathway in order to ensure timely diagnosis.

Sarcoma is a rare cancer originating in connective tissue, and treatment should be centralized to highly specialized sarcoma centers (Clasby et al. 1997, Rydholm. 1998, Bhangu et al. 2004). Magnetic resonance imaging (MRI) is the preferred diagnostic imaging modality for patients with suspected sarcoma (Bloem et al. 1997, Gielen et al. 2004). Furthermore, computed tomography (CT) has a place in the diagnostic work-up of bone tumors and tumors of the pelvis and abdomen, and is also used for staging (Grimer et al. 2010, Ilaslan et al. 2010).

In recent years, much attention has been given to fast-track diagnostic pathways when malignancy is suspected, to ensure timely diagnosis, and these have been implemented in some countries, including Denmark (Prades et al. 2011, Styring et al. 2012, Probst et al. 2012, National Institute for Health and Excellence (NICE) 2015). The conversion rate (the number of fast-track referrals resulting in a cancer diagnosis) is important for a fast-track referral program. It should be high enough to prevent overburdening of specialist centers, and low enough to ensure that general practitioners (GPs) can refer patients without barriers. All diagnostic programs for suspected sarcoma patients include imaging investigations with MRI/CT; however, the timing of these investigations differs. In Denmark, the patient must be investigated with imaging locally before being referred to a sarcoma center, but these investigations are not part of the urgent referral pathway (Sundhedsstyrelsen. 2012). On the other hand, in Sweden, direct referral based on clinical suspicion alone is advocated (Styring et al. 2012). Until 2015, English NICE guidelines stated that a patient suspected of sarcoma should be seen by a specialist within 2 weeks without imaging, but a pre-referral ultrasound has recently been included in the guidelines. Imaging at local hospitals prior to referral has been shown to reduce the number of referrals (Rowbotham et al. 2012), but it may also delay the diagnosis (Ashwood et al. 2003).

The effects of pre-referral investigations on time intervals and conversion rates in suspected sarcoma have not been investigated in a Danish setting. We wanted to investigate differences in time intervals and proportions of malignancies (i.e. conversion rates) in patients who were referred from outside the Aarhus uptake area after MRI and/or CT and/or histology was performed locally and in patients who were referred from Aarhus uptake area without having undergone any of these investigations. Furthermore, we assessed the extent of repeated scans.

Patients and methods

Setting

Sarcoma diagnostics and treatment are based at 2 centers in Denmark. Aarhus Sarcoma Center (ASC) handles all referrals from the Jutland region (with approximately 2.5 million inhabitants). On the January 1, 2009, the cancer patient pathway (CPP) for sarcomas was officially implemented in Denmark (Probst et al. 2012). The CPP is a fast-track referral system that describes the ideal way through the healthcare system for a patient suspected of having a sarcoma. The CPP defines which alarm symptoms/criteria should give suspicion of sarcoma and result in prompt referral for further diagnostics. Upon discovery of symptoms, the GP should refer to the local orthopedics department for clinical evaluation and imaging. The patient should be referred to ASC only when the suspicion has been justified by imaging and clinical evaluation at a local hospital. The fast-track pathway starts when the referral is received at the Sarcoma Center. This is the main official sarcoma CPP referral pathway.

However, for patients who reside in the local uptake area of Aarhus University Hospital, the orthopedics department containing ASC is the local orthopedics department. The GPs in this area may therefore refer directly to the Sarcoma Center without pre-referral scans. This referral pathway is also in accordance with the CPP. This enabled us to compare the 2 official CPP referral pathways for sarcomas, one with patients who were referred based on imaging and one with patients who were referred based on clinical suspicion.

Study population and data collection

All patients consecutively referred to the sarcoma CPP in the period September 1, 2014 to August 31, 2015 were invited to participate. Data were collected from patient and GP questionnaires and from patient records. The questionnaires were developed based on similar questionnaires for other forms of cancer (Jensen et al. 2014a) and were pilot tested to ensure that they could be understood. The patients received the questionnaires by mail before their first Sarcoma Center appointment. After giving informed consent, the patients underwent a short interview based on the questionnaire. The GP questionnaire was sent out if the patient or the patient record indicated

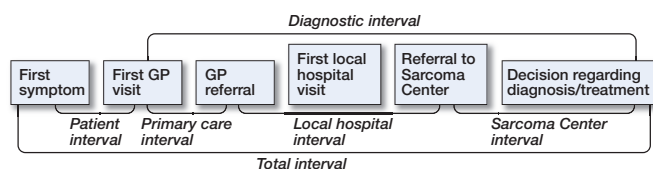


Figure 1. Overview of time intervals in the diagnostic process for patients suspected of having sarcoma (Weller et al. 2012).

that the GP had been involved. No remuneration was given to GPs. If necessary, a reminder with a new questionnaire was sent after 4–5 weeks, with a telephone reminder after a further 3 weeks. Data from local hospitals were collected by tracing the diagnostic route backwards through the patient records.

Variables

Final diagnosis was collected from the pathology report if the tumor had been biopsied/removed, and from the consensus decision based on imaging, clinical evaluation, and follow-up if the tumor had not been removed. Tumor size was measured as the largest diameter at the diagnostic MRI. Trojani grade-II and grade-III sarcomas were classified as high-grade tumors, and borderline and Trojani grade-I tumors were classified as low-grade tumors.

Information on GP investigations was collected from the GP questionnaires, in which the GP was asked to specify which diagnostic investigations he/she had requested. Details of diagnostic investigations at local hospitals and ASC were collected from the patient records.

Dates regarding the diagnostic process were given by the patient, the GP, the local hospital, and ASC. We defined 6 time intervals based on guidance from the Aarhus Statement (Weller et al. 2012): patient interval, primary care interval, local hospital interval, Sarcoma Center interval, diagnostic interval, and total interval (Figure 1). Specifically, the local hospital interval was defined as the time from referral to the first local hospital to final referral to the Sarcoma Center. The Sarcoma Center interval was calculated as the time from referral being received at the Sarcoma Center to the date on which a decision on the final course of treatment was taken (a decision regarding the final treatment modality or a decision not to treat). This decision date was also the endpoint of the diagnostic and total interval, and was chosen to ensure comparativeness regardless of the final diagnosis. The treatment interval was therefore not included. If a date was only reported as month and year, the fifteenth of that month was used. If only a year was stated, July 1 was used. For patients with missing GP data, the patient-reported date of the first visit to the doctor was used to calculate patient interval and diagnostic interval. Intervals were measured in calendar days.

Statistics

Descriptive statistics were used to calculate participation rates. Differences between groups were tested with chi-squared test

Table 1. Number of days—presented as median and interquartile interval (IQI)—spent in each phase of the diagnostic process from first symptom to decision regarding diagnosis/treatment, according to the referral pathway used

Referral pathway	n	Patient interval	Primary care interval	Local hospital interval	Sarcoma Center interval	Diagnostic interval	Total interval
Referred from Aarhus local uptake area							
with MRI/CT/histology	52	41 (10–368)	32 (13–80)	28 (14–105)	14 (8–21)	72 (32–179)	189 (65–837)
without MRI/CT/histology	91	45 (18–247)	1 (1–13)	8 (1–19)	18 (13–29)	29 (16–50)	93 (49–356)
Referred from outside Aarhus uptake area							
with MRI/CT/histology	357	59 (12–241)	11 (1–45)	29 (15–60)	15 (9–22)	59 (36–117)	166 (73–465)
without MRI/CT/histology	45	36 (8–135)	2 (1–16)	15 (12–30)	15 (9–23)	28 (17–50)	64 (35–210)

for categorical variables and Wilcoxon rank sum test was used for continuous variables. For comparison of time intervals, the population was divided into groups according to whether or not they were referred from the Aarhus area and whether or not they had been investigated with an MRI and/or CT and/or histology. Time intervals were not normally distributed, and are reported as medians with interquartile intervals (IQIs). Comparisons of time intervals between groups were done at the fiftieth and seventy-fifth percentile with quantile regression analyses, using the procedure written by Miranda (2006). Sex distribution was equal in all groups, and was not adjusted for in the final model. Age differed between groups and was adjusted for as a categorical variable (< 20, 20–39, 40–59, and ≥ 60 years). The quantile regression was repeated with inclusion of gender as a confounder in addition to age, and this had little or no effect on our estimates, assuring us that we could exclude sex in the final analysis. Thus, only age was adjusted for in the regression analyses presented in this paper. Any p-values of 0.05 or less were considered statistically significant. Analyses were performed using Stata statistical software version 13.

Ethics

The study was approved by the Danish Data Protection Agency (journal entry number 2007-58-0010), and all patients provided written consent. Approval from the Committee on Health Research Ethics of the Central Denmark Region was not necessary as no biomedical intervention was performed, according to Danish Law.

Results

Patient and GP participation

607 patients entered the CPP during the study period. Of these, 545 patients (90%) accepted participation. Of 62 non-participants, 56 did not wish to participate, 5 were not mentally able to answer questionnaires, and 1 did not speak Danish or English. The patients who did not participate did not differ statistically significantly from participants regarding age or sex distribution. Of the 466 GP questionnaires distrib-

uted, 400 (86%) were returned. For a further 42 patients (9%) with non-responding GPs, information on dates and imaging investigations performed were retrieved from the referral or the patient records.

Patient characteristics

Of the 102 sarcoma patients, 88 had a soft tissue sarcoma and 14 had a bone sarcoma. 40 of 545 patients were referred after a histology report indicated a diagnosis of sarcoma (after surgical excision or needle biopsy). 385 patients had had a CT and/or an MRI before referral. Of the 545 patients, 143 (26%) were referred from the local uptake area of Aarhus University Hospital. 91 (17%) were referred from the local area without pre-referral MRI and/or CT and/or histology, and 357 (66%) were referred from outside the local uptake area after investigation with MRI and/or CT and/or histology (Table 1). The percentage of women was 48%, and was similar between referral groups. Median age was 55 (0–93) years. 56 patients were under 18 years of age, 8 of whom had a sarcoma and 8 of whom had other malignancies.

Time intervals

Table 1 gives medians and IQIs for the time intervals for the 4 different referral groups. The time intervals of the 2 groups that followed the official referral pathway outlined in the CPP for sarcomas are compared in Table 2. The median patient interval was not statistically significantly different between groups. The primary care interval, local hospital interval, diagnostic interval, and total interval were all statistically significantly longer in the outside group referred after MRI/CT or histology. The difference in the diagnostic interval is illustrated in Figure 2.

Conversion rates and tumor size

Overall, 102 patients (19%) had a sarcoma and 68 (13%) were diagnosed with other malignancies, giving a total number of malignancies of 170 (31%). The proportions of malignancies in the different referral pathway groups are presented in Table 3. There was a statistically significantly higher proportion of malignancies and sarcomas in the outside group referred after MRI/CT or histology than in the group referred from the local

Table 2. Estimated difference in time intervals between patients who were referred from outside the Aarhus local uptake area after MRI and/or CT and/or histology performed locally and patients who were referred from Aarhus local uptake area without MRI and/or CT and/or histology performed locally. Measured as the difference in calendar days at the 50th percentile and 75th percentile with 95% confidence intervals (CIs), calculated by quantile regression

Percentile ^a	Patient interval	Primary care interval	Local hospital interval	Sarcoma Center interval	Diagnostic interval	Total interval
50th ^a	13 (0 to 27)	14 (9 to 19) ^b	27 (16 to 38) ^b	-3 (-7 to 1)	41 (30 to 51) ^b	91 (76 to 106) ^b
75th ^a	-47 (-61 to -32) ^b	37 (27 to 48) ^b	51 (36 to 65) ^b	-6 (-8 to -4) ^b	61 (29 to 94) ^b	110 (95 to 124) ^b

^a All analyses adjusted for age.
^b Statistical significance at the 5% level.

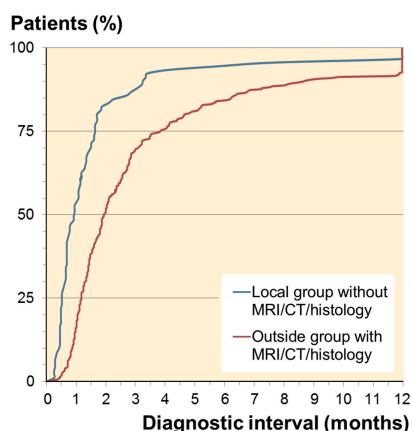


Figure 2. Cumulative frequencies of diagnostic interval in the local Aarhus area group of patients who were referred without pre-referral MRI/CT or histology and the outside group who were referred after pre-referral MRI/CT or histology. For the purposes of illustration, diagnostic intervals exceeding 365 days have been plotted as 12 months.

area without pre-referral MRI/CT or histological diagnosis ($p < 0.001$).

There was a trend of smaller tumor size in patients who were referred from Aarhus local area without MRI/CT or histology (median 3 cm) than in patients who were referred from the outside area with MRI/CT or histology (median 4 cm) ($p = 0.08$). When we compared tumor size between all the patients who were referred from the Aarhus local area and all the patients who were referred from the outside area regardless of investigations performed, the difference in tumor size was statistically significant ($p = 0.02$).

Proportion of repeated scans

345 patients (63%) were referred with an MRI-scan, and 78 patients (14%) were referred with a CT-scan. 38 patients (7%) were referred with both types of scan. 19 of the 345 MRI-scans had been repeated locally before referral because the initial scan was without contrast. 12 of the 345 MRI-scans had to be repeated at the Sarcoma Center before any decision on diagnosis/treatment. None of the CT-scans had to be repeated.

Table 3. Proportion of malignancies and sarcomas, according to the referral pathway used

Referral pathway	Proportion of malignancies ^a n (%)	Proportion of sarcomas n (%)
Referred from Aarhus local uptake area with MRI or CT or histology	13 of 52 (25)	9 of 52 (17)
Referred from Aarhus local uptake area without MRI or CT or histology	13 of 91 (14)	6 of 91 (7)
Referred from outside Aarhus local uptake area with MRI or CT or histology	134 of 357 (38)	84 of 357 (24)
Referred from outside Aarhus local uptake area without MRI or CT or histology	10 of 45 (22)	3 of 45 (7)

^a Includes all sarcomas and other malignancies.

Discussion

Main results

Median time from first symptom to decision regarding diagnosis/treatment was 91 days longer for patients referred after MRI/CT or histology at local hospitals outside Aarhus uptake area than for patients who were referred without these investigations from the local Aarhus uptake area. The median diagnostic interval was 41 days longer in the outside group, due both to longer primary care and to local hospital intervals. This indicates that when pre-referral imaging is not part of the urgent referral pathway, both access to investigation and the speed of investigations are compromised. The conversion rate was 2-fold higher in the patient group investigated with MRI/CT or histology (38% vs. 14%). Only 3.5% of MRI-scans performed locally before referral had to be repeated at the Sarcoma Center.

Comparison with the literature

Conversion rates in fast-track pathways for musculoskeletal sarcomas differ between countries. A London-based study found that 2% of patients who were referred on the basis of clinical features alone had a sarcoma, compared to 17% of patients who were referred after local investigations (Pencavel

et al. 2010). In Birmingham, 13% of patients who were referred based on clinical suspicion of sarcoma alone had a malignancy, as apposed to 49% of the patients who were referred after imaging (Taylor et al. 2010). Smolle et al. (2015) surprisingly found a higher proportion of malignancy in patients who were referred without imaging, and they attributed this to more obvious symptoms (confounding by severity). This may also have been the reason for the fairly high proportion of malignancies in our groups that were referred without imaging. In Sweden, no pre-referral imaging is required and a malignancy proportion of 24% (16% sarcoma) has been reported (Styring et al. 2012), which is higher than what we found (13%; 6% sarcoma). However, several patients in the Swedish study had undergone pre-referral imaging. In accordance with other studies, our results show that pre-referral investigations can reduce the number of referrals (Pencavel et al. 2010, Rowbotham et al. 2012, Shah et al. 2015). We did not find a high proportion of repeated scans, as reported from other countries (Ashwood et al. 2003, Styring et al. 2012). Our finding of a larger tumor size and higher malignancy grade in patients referred from the outside area might indicate a negative effect of longer waiting time. However, the number of patients in each group was small, so these results should be interpreted with caution and any direct causality cannot be inferred based on our numbers.

In contrast to the benefit of a higher conversion rate, there is the lengthening of time intervals for patients who are referred after local imaging investigations. The difference in diagnostic interval was 41 days at the median and 91 days at the seventy-fifth percentile, indicating that the difference in waiting times is more pronounced in the 25% of patients who have the longest wait. Other studies have shown that local investigations before referral produce delay for cancer patients (Ashwood et al. 2003, Styring et al. 2012, van der Geest et al. 2014, Rubin et al. 2015), and direct referral of suspected sarcoma patients has been suggested by other authors (Ashwood et al. 2003, Seinen et al. 2010, Styring et al. 2012). Although the CPP for sarcomas reduced the waiting times at ASC (Dyrop et al. 2013), the waiting times that occur locally outside ASC are still very long. The Danish CPP contains no time limits for the diagnostic process at local hospitals, and our results show that when the CPP for sarcoma does not include pre-referral imaging as a part of the fast-track program, a large group of patients have a delayed diagnosis. The main change following CPP implementation in Denmark was a shift from serial investigations to parallel investigations, but starting only when the patient is seen at the Sarcoma Center and thus not at local hospitals. Investigations in primary care and at local hospitals are still done in a serial manner, according to the same waiting time regulations and the same limited access to imaging as before implementation of the CPP.

The waiting time before diagnosis for patients who reside outside Aarhus uptake area could be reduced by removing the demand for local MRI/CT investigations before referral to the CPP. However, this might overburden the scanner capacity of

the Sarcoma Center. Other possibilities would be to extend CPP time limits to include the local hospital work-up, or to improve GPs' access to diagnostics at local hospitals. In Denmark, only hospital physicians can order an MRI or a CT of tumors; GPs have no direct powers of referral. Better access to imaging for GPs has been suggested as the way forward in Danish cancer diagnostics (Guldbrandt et al. 2013, Hjertholm et al. 2014, Jensen et al. 2014b), but reports on such initiatives differ. In the UK, primary care investigations substantially lengthened the primary care interval for cancer patients without reducing referral delay (Rubin et al. 2015). A Danish trial on direct access of GPs to chest CTs for patients suspected of having lung cancer showed unchanged CT usage and a decrease in specialist time spent per patient (Guldbrandt et al. 2013). This solution may be worth exploring for suspected sarcoma patients in Denmark.

Strengths and limitations

Our results were strengthened by the high participation rate and the completeness of data. Age and sex were not significantly different between participants and non-participants; however, we could not obtain any information on the proportion of malignancies or time intervals for non-participants. The direction of any selection bias cannot be evaluated, but the small number of non-participants limited the effect. The primary care interval could have been underestimated if non-responding GPs were reluctant to answer because of long delays. For calculation of patient interval and diagnostic interval, the patient's date for the first doctor's visit was used for patients whose GPs did not respond, to minimize this problem. Patient-reported data were validated with interviews to improve the completeness and quality of data. GPs were asked to consult the patient records when answering questionnaires, to reduce recall bias. Our results should be interpreted with referral bias in mind, as we only have data on patients who were referred to the fast-track pathway. It is fairly certain that all the sarcoma patients were referred, but there was a large population of patients with benign conditions and other malignancies who were not referred.

Conclusions

Pre-referral investigations at a local hospital increased the diagnostic interval by at least 1 month for 50% of the patients. The conversion rate was more than doubled, to almost 40%. If investigations are to be performed before referral to a sarcoma center, these investigations should be part of the fast-track pathway to ensure timely diagnosis. In future, efforts should be put into providing easier access to imaging and reducing the time spent at local hospitals before referral.

The study was funded by grants from "A.P. Møller og Hustru Chastine Mc-Kinney Møllers Fond til almene Formaal", "Radiumstationens forskningsfond", and "Max og Inger Wørzners Mindelegat".

Design: HBD, PV, AS, and JK. Data collection: HBD and MR. Statistical analysis and writing of first draft: HBD. All the authors participated in interpretation of the results and revision of the manuscript.

We are grateful to the patients and GPs who participated. We also thank the physicians, nurses, and secretaries at Aarhus Sarcoma Center for their assistance.

- Ashwood N, Witt J D, Hallam P J, Cobb J P. Analysis of the referral pattern to a supraregional bone and soft tissue tumour service. *Ann R Coll Surg Engl* 2003; 85 (4): 272-6.
- Bhangu A A, Beard J A, Grimer R J. Should soft tissue sarcomas be treated at a specialist centre? *Sarcoma* 2004; 8 (1): 1-6.
- Bloem J L, van der Woude H J, Geirnaerd M, Hogendoorn P C, Taminiou A H, Hermans J. Does magnetic resonance imaging make a difference for patients with musculoskeletal sarcoma? *Br J Radiol* 1997; 70 (832): 327-37.
- Clasby R, Tilling K, Smith M A, Fletcher C D. Variable management of soft tissue sarcoma: Regional audit with implications for specialist care. *Br J Surg* 1997; 84 (12): 1692-6.
- Dyrop H B, Safwat A, Vedsted P, Maretty-Nielsen K, Hansen B H, Jorgensen P H, Baad-Hansen T, Bunge C, Keller J. Cancer patient pathways shorten waiting times and accelerates the diagnostic process of suspected sarcoma patients in Denmark. *Health Policy* 2013; 113 (1-2): 110-7.
- Gielen J L, De Schepper A M, Vanhoenacker F, Parizel P M, Wang X L, Sciort R, Weyler J. Accuracy of MRI in characterization of soft tissue tumors and tumor-like lesions. A prospective study in 548 patients. *Eur Radiol* 2004; 14 (12): 2320-30.
- Grimer R, Judson I, Peake D, Seddon B. Guidelines for the management of soft tissue sarcomas. *Sarcoma* 2010; 2010: 506182.
- Guldbrandt L M, Fenger-Gron M, Folkersen B H, Rasmussen T R, Vedsted P. Reduced specialist time with direct computed tomography for suspected lung cancer in primary care. *Dan Med J* 2013; 60 (12): A4738.
- Hjertholm P, Moth G, Ingeman M L, Vedsted P. Predictive values of GPs' suspicion of serious disease: A population-based follow-up study. *Br J Gen Pract* 2014; 64 (623): e346-53.
- Ilaslan H, Schils J, Nageotte W, Lietman S A, Sundaram M. Clinical presentation and imaging of bone and soft-tissue sarcomas. *Cleve Clin J Med* 2010; 77 Suppl 1: S2-7.
- Jensen H, Topping M L, Larsen M B, Vedsted P. Existing data sources for clinical epidemiology: Danish cancer in primary care cohort. *Clin Epidemiol* 2014a; 6: 237-46.
- Jensen H, Topping M L, Olesen F, Overgaard J, Vedsted P. Cancer suspicion in general practice, urgent referral and time to diagnosis: A population-based GP survey and registry study. *BMC Cancer* 2014b; 14: 636,2407-14-636.
- Miranda A. QCOUNT: Stata program to fit quantile regression models for count data. Boston College Department of Economics. 2006
- National Institute for Health and Excellence (NICE). Referral guidelines for suspected cancer - NICE guideline 27. National Institute for Health and Excellence (NICE) 2015
- Pencavel T D, Strauss D C, Thomas G P, Thomas J M, Hayes A J. Does the two-week rule pathway improve the diagnosis of soft tissue sarcoma? A retrospective review of referral patterns and outcomes over five years in a regional sarcoma centre. *Ann R Coll Surg Engl* 2010; 92 (5): 417-21.
- Prades J, Espinas J A, Font R, Argimon J M, Borrás J M. Implementing a cancer fast-track programme between primary and specialised care in Catalonia (Spain): A mixed methods study. *Br J Cancer* 2011; 105 (6): 753-9.
- Probst H B, Hussain Z B, Andersen O. Cancer patient pathways in Denmark as a joint effort between bureaucrats, health professionals and politicians--a national Danish project. *Health Policy* 2012; 105 (1): 65-70.
- Rowbotham E, Bhuvra S, Gupta H, Robinson P. Assessment of referrals into the soft tissue sarcoma service: Evaluation of imaging early in the pathway process. *Sarcoma* 2012; 2012: 781723.
- Rubin G P, Saunders C L, Abel G A, McPhail S, Lyrtzopoulos G, Neal R D. Impact of investigations in general practice on timeliness of referral for patients subsequently diagnosed with cancer: Analysis of national primary care audit data. *Br J Cancer* 2015; 112 (4): 676-87.
- Rydholm A. Improving the management of soft tissue sarcoma. Diagnosis and treatment should be given in specialist centres. *BMJ* 1998; 317 (7151): 93-4.
- Seinen J, Almquist M, Styring E, Rydholm A, Nilbert M. Delays in the management of retroperitoneal sarcomas. *Sarcoma* 2010; 2010: 702573.
- Shah A, Botchu R, Ashford R U, Rennie W J. Diagnostic triage for sarcoma: An effective model for reducing referrals to the sarcoma multidisciplinary team. *Br J Radiol* 2015; 88 (1049): 20150037.
- Smolle M A, Leithner A, Grimer R J. Evaluating the British sarcoma referral form. *Ann R Coll Surg Engl* 2015; 97 (6): 434-8.
- Styring E, Billing V, Hartman L, Nilbert M, Seinen J M, Veurink N, Vult von Steyern F, Rydholm A. Simple guidelines for efficient referral of soft-tissue sarcomas: A population-based evaluation of adherence to guidelines and referral patterns. *J Bone Joint Surg Am* 2012; 94 (14): 1291-6.
- Sundhedsstyrelsen. Pakkeforløb for sarkomer i knogle og bløddede. 2012;
- Taylor W S, Grimer R J, Carter S R, Tillman R M, Abudu A, Jeys L. "Two-week waits"-are they leading to earlier diagnosis of soft-tissue sarcomas? *Sarcoma* 2010; 2010: 312648.
- van der Geest L G, Elferink M A, Steup W H, Witte A M, Nortier J W, Tolenaar R A, Struikmans H. Guidelines-based diagnostic process does increase hospital delay in a cohort of colorectal cancer patients: A population-based study. *Eur J Cancer Prev* 2014; 23 (5): 344-52.
- Weller D, Vedsted P, Rubin G, Walter F M, Emery J, Scott S, Campbell C, Andersen R S, Hamilton W, Olesen F, Rose P, Nafees S, van Rijswijk E, Hiom S, Muth C, Beyer M, Neal R D. The Aarhus statement: Improving design and reporting of studies on early cancer diagnosis. *Br J Cancer* 2012; 106 (7): 1262-7.